UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/583,135	12/26/2006	Bernard Weill	292043US0X PCT	4938

22850 7590 10/22/2010

OBLON, SPIVAK, MCCLELLAND MAIER & NEUSTADT, L.L.P.
1940 DUKE STREET
ALEXANDRIA, VA 22314

EXAMINER	
FRAZIER, BARBARA S	
ART UNIT	PAPER NUMBER
1611	

NOTIFICATION DATE	DELIVERY MODE
10/22/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentdocket@oblon.com
oblonpat@oblon.com
jgardner@oblon.com

Office Action Summary	Application No.	Applicant(s)	
	10/583,135	WEILL ET AL.	
	Examiner	Art Unit	
	BARBARA FRAZIER	1611	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 August 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8,10 and 11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8,10 and 11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

1. Claims 8, 10, and 11 are pending in this application.

2. Claims 8, 10, and 11 are examined.

Specification

3. The objection to the disclosure is withdrawn in view of Applicant's amendment to the disclosure.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 8, 10, and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Crapo et al (WO 02/060383, cited by Applicants) in view of Brurok et al (Biochem. Biophys. Res. Comm., 254:768-772, 1999) and Towart et al (WO 97/049390, cited by Applicants).

The claimed invention is drawn to a method for increasing the cytostatic or cytotoxic effects on tumor cells, and decreasing the cytotoxic effect on normal leucocytes of an anticancer medicinal product comprising one or more platinum

derivative, wherein said method comprises administering to a patient treated with said anticancer medicinal product, an antitumoral and leukocyte-protecting amount of mangafodipir and wherein said platinum derivative is cisplatin or oxaliplatin (see claim 8). The amount of mangafodipir administered to said patient is from 1 to 100 mg/kg/day (claim 10). Also claimed is a composition comprising mangafodipir and cisplatin or oxaliplatin (claim 11).

Crapo et al teach a method of preventing or treating cancer using mimetics of superoxide dismutase (SOD) as the active agent or as a chemo- and/or radio protectant (abstract and page 7). Crapo et al teach various manganese-containing SOD mimetics which may be used as the SOD mimetic, including porphines and tetrapyrroles; manganese derivatives are preferred (pages 7 and 8). The compounds can be used in combination with other chemotherapeutic agents, such as bleomycin, **cisplatin**, adriamycin, and camptothicen; when used in combination therapy, the compounds can increase the anti-tumor effect of chemotherapy as well as prevent toxicity, in whole or in part, resulting from free radicals produced by agents such as bleomycin, **cisplatin**, and adriamycin (pages 8-9). Normal tissues which can be protected include leucocytes (page 9).

While Crapo et al teach the use of manganese-containing SOD mimetics, Crapo et al do not specifically teach that the manganese-containing SOD mimetic is mangafodipir (MnDPDP).

Brurok et al teach that MnDPDP possesses SOD mimetic activities (e.g., see abstract and page 768), as evidenced by reduced spin adduct formation with EST/DMPO, and by maintained urate production (pages 770-771).

Towart et al teach that dipyridoxyl based chelating agents, particularly manganese containing compounds are particularly effective in reducing the toxicity of anti-tumor agents (pages 2 and 3); MnDPDP is more particularly preferred (page 7).

It would have been obvious to a person having ordinary skill in the art at the time the invention was made to substitute MnDPDP (mangafodipir) for one of the manganese-containing SOD mimetics taught in the methods of Crapo et al; thus arriving at the claimed invention. One skilled in the art would be motivated to do so, with a reasonable expectation of success, because mangafodipir is also known to possess SOD-mimetic activity, as taught by Brurok et al, and therefore is known to be functionally equivalent to the SOD-mimetics specifically taught by Crapo et al. Furthermore, mangafodipir is known to reduce the toxicity of an antitumor agent, and is "particularly preferred" for this purpose, as taught by Towart et al. Therefore, since mangafodipir possesses the properties of being a manganese-containing SOD mimetic as well as chemoprotective activity, it would be within the purview of the skilled artisan to substitute a compound of similar structure and activity (i.e., mangafodipir) for one of the compounds specifically taught by Crapo et al, with a reasonable expectation of success. Further, one skilled in the art would be motivated to make such a substitution since mangafodipir is particularly preferred for its chemoprotective activity.

Response to Arguments

6. Applicant's arguments filed 09 August 2010 have been fully considered but they are not persuasive.

Applicants argue that only one example of the seven total disclosed in Crapo relates to the study of the effects of the use of a SOD mimetic in a treatment with another chemotherapeutic agent, where example 3 illustrates that MnTBAP allows attenuating bleomycin-induced lung fibrosis in mice. Applicants assert that Crapo provides no motivation and/or expectation of success in using a SOD mimetic with another anti-tumor agent other than bleomycin (page 5 of Applicant's Remarks). Applicants argue that Crapo fails to provide any reasonable basis for using a SOD mimetic with another anti-tumor agent other than bleomycin and does not provide any suggestion of associating a SOD mimetic specifically with cisplatin or oxaliplatin (pages 6-7 of Remarks).

This argument is not persuasive. Disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments. *In re Susi*, 440 F.2d 442, 169 USPQ 423 (CCPA 1971). Crapo teaches that its SOD mimetics can be used in combination with other chemotherapeutic agents, such as bleomycin, **cisplatin**, adriamycin, and camptothicen; when used in combination therapy, the compounds can increase the anti-tumor effect of chemotherapy as well as prevent toxicity, in whole or in part, resulting from free radicals produced by agents such as bleomycin, **cisplatin**, and adriamycin (pages 8-9). Therefore, one skilled in the art would reasonably expect success from using its SOD

mimetics with any of the chemotherapeutic agents named by Crapo, since the use of any of the four chemotherapeutic agents named by Crapo amounts to choosing from a finite list of identified, predictable solutions.

Regarding the teachings of Towart, Applicants argue 1) Towart discloses that chelating agents including mangafodipir are effective in reducing the cardiotoxicity of paclitaxel and anthracyclines, such as doxorubicin, but does not disclose or suggest that mangafodipir may be useful in combination with other antitumor agents than anthracyclines and paclitaxel (page 4 of Applicant's Remarks); 2) Towart indicates that the use of metal chelates can make it possible to increase the effectiveness of the treatment by administering higher amounts of the antitumor agent with which they are associated, instead of increasing the effectiveness of the treatment without increasing the amounts of the other anti-tumor agent, as in the claimed invention; 3) Towart fails to disclose or suggest any protective effect on leucocytes by mangafodipir, and direct the skilled artisan away from the association of compounds according to the present invention; and 4) Towart is concerned with pathological condition in which the heart is at risk, which is quite different from obtaining a protective effect on normal leucocytes in an anti-cancer chemotherapy combined with an increased cytotoxic effect on tumor cells (pages 5-6 of Applicant's remarks).

These arguments are not persuasive. Regarding 1), Towart teaches certain metal chelates, of which mangafodipir is particularly preferred, are particularly effective in reducing the toxicity of anti-tumor agents (pages 2-3), and states, "a number of anti-tumor agents are associated with adverse side-effects which severely limit their

widespread use." (Page 1). Paclitaxel and anthracyclines are listed as particular examples (page 3). Disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments. *In re Susi*, 440 F.2d 442, 169 USPQ 423 (CCPA 1971). Therefore, one skilled in the art would be motivated to select mangafodipir as the SOD mimetic of Crapo because of its ability to reduce the toxicity of anti-tumor agents. Regarding 2), it is noted that Towart is still directed to the use of mangafodipir to provide protective effects from the use of an anti-tumor agent, and Applicant's claims are not limited to any particular amount of mangafodipir or antitumor agent, and therefore the teachings of Towart provide motivation to one skilled in the art to use mangafodipir in the invention of Crapo et al, with a reasonable expectation of success. Regarding 3) and 4), it is noted that the rejection is not based upon the teachings of Towart alone, but rather the teachings of Crapo in view of Towart and Brurok. Crapo already teaches that the use of SOD mimetics protects a wide variety of normal tissues, including leucocytes (page 9). The teachings of Towart are relied upon to show that one skilled in the art would be further motivated to selected mangafodipir as the SOD mimetic used in Crapo since it also provides cardioprotective benefits when used with antitumor agents. Towart need not teach protective effect for leucocytes, since this is already taught by Crapo. That Towart teaches co-administration of a hematopoietic growth factor (G-CSF) with paclitaxel to reduce myelotoxicity does not direct the skilled artisan away from the association of mangafodipir with an antitumor agent, since Towart still teaches co-administration of mangafodipir with an antitumor agent, and Towart does not specifically

teach that mangafodipir would not reduce myelotoxicity, or interfere with its reduction when co-administered with G-CSF.

Applicants argue that unexpected results are obtained with the method and the pharmaceutical composition of the claimed invention, citing Examples 2, 3, and 7 of the specification. Applicants argue that nothing in the cited art suggested that mangafodipir with either cisplatin or oxaliplatin would allow for an increase in the cytostatic or cytotoxic effects on tumor cells and for a decrease of the cytotoxic effect on normal leucocytes of an anticancer medicinal product

This argument is not persuasive. Applicant's data in the specification has been fully considered, but is not persuasive for overcoming the rejection. Crapo already teaches that SOD mimetic compounds can be used in combination with other chemotherapeutic agents, such as bleomycin, **cisplatin**, adriamycin, and camptothicen; when used in combination therapy, the compounds can increase the anti-tumor effect of chemotherapy as well as prevent toxicity, in whole or in part, resulting from free radicals produced by agents such as bleomycin, **cisplatin**, and adriamycin (pages 8-9). Since mangafodipir is a known SOD mimetic as evidenced by Brurok, it would be within the purview of the skilled artisan to select a SOD mimetic from those known in order to optimize the anti-tumor effect of the combination therapy as taught by Crapo. Therefore, the results obtained in Applicant's specification are neither surprising nor unexpected.

Therefore, it is the Examiner's position that the claims are rendered obvious.

Conclusion

No claims are allowed at this time.

7. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to BARBARA FRAZIER whose telephone number is (571)270-3496. The examiner can normally be reached on Monday-Thursday 9am-4pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sharmila Landau can be reached on (571)272-0614. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

BSF

/Ashwin Mehta/
Primary Examiner, Technology Center 1600